A retrospective review of paediatric cryptococcosis in three academic hospitals in Johannesburg, 2002-2011.

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Declaration

I, Fikile Cynthia Mabena declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Paediatrics in the University of the Witwatersrand. It has not been submitted before for any degree or examination at this or any other University.

On --------- day of ---------- 2015

Dedication

For my daughter, Langelihle Dube, my husband Pallo Marumo and my parents Ntlhakane and Joe Mabena.

Abstract

Aim:

To describe the demographics, management and outcomes of children admitted with laboratory-confirmed cryptococcosis at three Johannesburg hospitals from 2002-2011.

Method:

Records of patients younger than 14 years of age who were diagnosed with cryptococcosis (as identified by review of the GERMS-SA surveillance) over the 10 year study period were reviewed using a structured data collection tool. The patients were managed in the Paediatric Departments at Chris Hani Baragwanath Academic Hospital (CHBAH), Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Rahima Moosa Mother and Child Hospital (RMMCH).

Results:

Forty-eight children under 14 years of age were included in this study. The median age was 9.6 years (Interquartile Range (IQR), 7.0 to 11.8 years), most of them (31/48, 64.6%) were boys and 27 (56.3%) were from CHBAH. Thirty-eight (79.2%) were HIV positive with very low CD4 counts (n=26; median 13 cells/mm^3; IQR, 5 to 144 cells/mm^3). Of the eight HIV negative patients, one had leukaemia, two were neonates and five had no known underlying predisposing condition.

Children with cryptococcosis presented for care mainly with headache (60.5%), vomiting (59.5%) and fever (43.2%). Twenty-four (50.0%) had cryptococcal meningitis, 14 (29.2%) had meningitis with concomitant cryptococcaemia, and 10 (20.8%) had cryptococcaemia without meningitis. Children with cryptococcal meningitis were 7.5-fold (95% CI, 1.31 to 51.93) more

likely to have been treated with amphotericin B compared to those who had fungaemia without meningitis, P=0.001.

Nineteen (39.6%) patients were started on anti-tuberculosis treatment during the course of their hospitalisation with cryptococcosis. Five (41.7%) of the 12 children on fluconazole and concomitant TB treatment were on boosted fluconazole dosage regimens (i.e., >10 mg/kg/day). Twelve (31.6%) of the 38 HIV positive children with cryptococcosis were not sent home on fluconazole prophylaxis.

Ten (20.8%) children died during the course of their hospital admission.

Conclusion:

Paediatric cryptococcosis is a rare condition. HIV infection is an important predisposing condition to cryptococcal disease. There appeared to be widespread deviation from published guidelines in terms of treating patients with fluconazole at public health facilities in Gauteng Province. Clinicians caring for children with cryptococcal disease should seek advice from infectious disease clinicians in order to optimise patient care.

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Nomenclature

ART	antiretroviral therapy
CDC	Centres for Disease Control and Prevention
CHBAH	Chris Hani Baragwanath Academic Hospital
CI	confidence interval
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CSF	cerebrospinal fluid
GCS	Glasgow Coma Scale
GERMS-SA	Group of Enteric, Respiratory and Meningeal Disease Surveillance in South Africa
HIV	human immunodeficiency virus
ICU	intensive care unit
IQR	interquartile range
IRIS	immune reconstitution inflammatory syndrome
LP	lumbar puncture
NHLS	National Health Laboratory Service
PHRU	Perinatal HIV Research Unit
RMMCH	Rahima Moosa Mother and Child Hospital

SD	standard deviation
WAZ	weight-for-age Z-score
WHO	World Health Organization

1.0: Introduction

1.1 **An overview of the pathogenic *Cryptococcus* species**

Cryptococcal disease is caused by the encapsulated yeast, *Cryptococcus*, of which the two most commonly pathogenic species are *Cryptococcus neoformans* and *Cryptococcus gattii*. These are closely-related pathogenic yeasts and *C. neoformans* usually causes disease among patients with HIV infection and other immune-deficiencies whereas *C. gattii* has been observed to cause disease among immunocompetent patients [1]. In Africa *C. gattii* has also been reported to cause disease in both immunocompromised and immunocompetent patients [2].

Cryptococcal disease is acquired through the inhalation of infectious particles found in the environment, usually associated with desiccated pigeon droppings [3]. The infection may remain dormant in the lung until such time as a patient becomes immune compromised, after which it may spread haematogenously to any part of the body. The disease spectrum includes infection of the bone, bloodstream, central nervous system, kidneys, liver, lymph nodes, skin and spleen [4, 5].

1.2 Cryptococcal Disease: Diagnosis, Clinical Manifestations and Treatment

Cryptococcal meningitis is the most common presentation of human immunodeficiency virus (HIV)-related cryptococcal disease among adults, and has case fatality ratios as high as 35%-65% in sub-Saharan Africa [6, 7]. The clinical presentation of cryptococcal meningitis among adults is typically that of a sub-acute meningitis with varying combinations of fever,

headache, nausea, vomiting and cognitive dysfunction [8] . Focal neurological signs and seizures may also be present [8]. The most significant markers for poor clinical outcomes are an altered mental status, a persistently raised intracranial pressure (>20 cm H_2O) and a CD4 count less than 100 cells/mm^3 [8].

A definitive diagnosis of cryptococcal meningitis is made through culture of *Cryptococcus* spp. in the cerebrospinal fluid (CSF). Alternative diagnostic approaches include India ink staining of CSF and the cryptococcal antigen test performed on blood and CSF specimens, which has a sensitivity of 95%, being more reliable than India ink staining [9, 10].

A standard treatment regimen employs the use of the antifungal agents amphotericin B in combination with either flucytosine (where available) or fluconazole, starting with a two-week induction phase of amphotericin B (1mg/kg/dose, administered as an intravenous infusion daily) followed by eight weeks of oral fluconazole[11]. A secondary prophylaxis phase of treatment follows in which oral fluconazole is given for life or until the patient's CD4 count is >200 cells/mm^3 for more than 12 months [9, 10]. Flucytosine, co-administrated with amphotericin B during the induction phase of treatment, is the treatment of choice according to international guidelines; however, flucytosine is not available in South Africa [10, 11].

In the developed world, with increased use of antiretroviral therapy (ART), the incidence of cryptococcal disease has decreased considerably amongst HIV-infected patients [7]. In resource-limited settings, treatment of HIV-positive patients with antiretrovirals often occurs when patients are already severely immunocompromised, and because cryptococcal disease occurs more commonly among patients with low CD4 counts (<100 cells/mm^3), the burden of the disease has remained high despite increasing access to ART [7, 12]. Cryptococcal disease still accounts for as many as 10%-20% of all deaths in HIV-positive cohorts in sub-Saharan Africa, causing an estimated 500,000 deaths annually in this region [13].

1.3 Paediatric Cryptococcal Disease

Cryptococcosis occurs among children but is unaccountably less common than among adults [14]. Even in sub-Saharan Africa which has the highest prevalence of co-infection with HIV and *Cryptococcus*, cryptococcosis is rare in children [15]. A report from Gauteng Province in South Africa documented a total of 2,753 cases of cryptococcosis between 2002 and 2004, with only 24 (0.9%) of those being younger than 15 years of age [15, 16]. A similar prevalence (1%) for childhood co-infection with HIV and *Cryptococcus* was estimated from early studies in the United States [14]. In a South African study comparing paediatric and adult-onset cryptococcosis from 2005-2007, there was a bimodal distribution of cryptococcal disease among children, firstly among neonates and infants, and secondly among school-going and adolescent children [17]. There is still a scarcity of data on perinatally-acquired, neonatal, and paediatric cryptococcosis, including its clinical presentation and management, as compared to adult cryptococcal disease [18, 19].

1.4 The Current Status of Cryptococcal Disease Treatment Guidelines

There are currently no specific treatment guidelines for children with cryptococcal disease, and treatment recommendations are based on data obtained through treating adults [10]. The World Health Organization (WHO) pocketbook of hospital care for children describes recommendations on the treatment of cryptococcal meningitis [20] and the WHO Rapid Advice document which was published in December 2011 also gives recommendations on the

diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children [11]. The WHO Rapid Advice document makes six key recommendations, based on data available for adults:

1. The diagnosis of cryptococcosis should be made early in severely immunocompromised patients through the use of lumbar puncture (LP) and cryptococcal antigen testing of CSF;
2. Primary prophylaxis (using oral fluconazole) is currently not recommended routinely in HIV-infected patients with CD4 counts <100 cell/mm^3, unless a prolonged delay in ART initiation is likely. Screening for *Cryptococcus* in adults (but not adolescents and children) with CD4 counts <100 cells/mm^3 before ART initiation and starting appropriate antifungal therapy is recommended, however;
3. For patients with cryptococcal disease, a treatment induction phase with amphotericin B and flucytosine (or fluconazole where flucytosine is not available) is recommended. Induction regimens with fluconazole and flucytocine or high-dose fluconazole monotherapy are recommended where amphotericin B is not available. An eight week consolidation phase of treatment with oral fluconazole, and secondary fluconazole prophylaxis are recommended after the induction phase;
4. Prevention, monitoring and management of amphotericin B toxicity is recommended to minimize hypokalaemia and nephrotoxicity associated with the use of amphotericin B;
5. ART should be started after four weeks of antifungal treatment in HIV-positive patients newly diagnosed with cryptococcosis. This recommendation safeguards against the adverse outcome of immune reconstitution inflammatory syndromes (IRIS) related to residual cryptococcal disease;

6. Secondary prophylaxis can be discontinued in HIV-positive adult patients with successfully treated cryptococcal disease after at least 12 months on the antifungal therapy, if they are adherent to ART and immune reconstituted [11].

Paediatric recommendations are similar to those for adults although the evidence base is not as robust. The Southern African HIV Clinicians' Society guidelines on the prevention, diagnosis and management of cryptococcal meningitis and disseminated cryptococcosis in HIV-positive adult patients [10] have been widely used in the Southern African region as a guide for the treatment of cryptococcosis among children.

1.5 Cryptococcal Surveillance

The National Institute for Communicable Diseases (NICD) has conducted ongoing population based surveillance for cryptococcal disease in South Africa since 2002. A comparison of paediatric and adult onset cryptococcosis detected through population-based surveillance in South Africa from 2005-2007 showed 361 (2.2%) of the 16,192 episodes of cryptococcosis in South Africa occurred among children (<15 years) and the highest incidence was documented in infants <12 months of age [17]. Although most patients with cryptococcosis were HIV-positive, there was a higher proportion of HIV-negative children (9%) compared to HIV-negative adults (1%) with cryptococcosis [17]. A United States study which described the profile of cryptococcal disease between 2003-2008 also showed that the majority (63.5%) of children hospitalised with cryptococcal disease were HIV-negative, however they did have other immunocompromising medical conditions, including malignancies, immunological disorders and organ transplantation [21].

1.6 Aim of the Study

The aim of the study was to describe the demographics, management and outcomes of children younger than 14 years admitted with laboratory-confirmed cryptococcosis at three Johannesburg hospitals in the decade spanning 2002-2011.

2.0: Methods

2.1 Design

A cross sectional retrospective review of records of patients who were diagnosed with cryptococcosis from 01 January 2002 to 31 December 2011 was done and their presentation, management and outcomes were described. Details of the children with a positive microbiological diagnosis of cryptococcosis were obtained with permission from Dr Govender of the National Institute for Communicable Diseases' GERMS-SA data-base. GERMS-SA is a nationwide active, prospective surveillance network which was established in 2005 in order to determine the epidemiologic trends of important infectious disease syndromes in South Africa [22].

All cryptococcal fungal isolates arising from the study site microbiology laboratories are routinely sent to the NICD, Sandringham, Johannesburg and a case report form detailing patient characteristics is captured. Surveillance officers (trained enrolled and professional nurses) collect additional clinical and epidemiologic information on the laboratory confirmed cases. Occasionally, 'audit cases' are identified whose cryptococcal isolates were not reported to GERMS-SA, however such 'audit cases' represent a small fraction of all cases, and it is generally regarded that GERMS-SA data relating to cryptococcal disease in South Africa is reasonably complete. GERMS-SA is thus able to provide essential public health information to the Department of Health and other stakeholders.

The names and specimen numbers of the children under 14 years of age with laboratory-confirmed cryptococcal disease, as identified through the GERMS database, were used to access the patients' clinical records and other blood results from the hospital records departments and the National Health Laboratory Service (NHLS) laboratory results system respectively. A manual review of the medical records was performed using a standardised data collection form (Appendix 1, page 43-48). Data collected included: demographics (age, gender), clinical presentation, co-morbidities (including HIV status and immunologic status (classified according to CD4 count) if available), treatment and outcomes.

2.2 Study Sites

The study was conducted at three academic Paediatric Departments, based in hospitals affiliated with the University of the Witwatersrand Faculty of Health Sciences in Johannesburg, South Africa. The hospitals include: Chris Hani Baragwanath Academic Hospital (CHBAH), Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Rahima Moosa Mother and Child Hospital (RMMCH).

2.2.1 Chris Hani Baragwanath Academic Hospital (CHBAH)

This is the largest hospital in the southern hemisphere with 2,888 approved beds, of which 2,639 are in use, and approximately 6,101 staff members (personal communication: B Phakathi, Data Manager, District Health System, CHBAH and Mrs L Roos, Principal personnel officer, Human Resources, CHBAH). It is located in Diepkloof, Soweto, south-west of

Johannesburg. The paediatric department has 371 paediatric beds, 58 of which are dedicated for haematology-oncology and cardiology. There are 134 neonatal beds including a 12-bed neonatal intensive care unit and 70 neonatal high-care beds. A further eight paediatric intensive care unit (ICU) beds are available in the general ICU. Approximately 65,000 outpatients are seen annually, including those seen at sub-specialty clinics (personal communication: B Phakathi, Data Manager, District Health System, CHBAH). The prevalence of HIV infection amongst the paediatric admissions at CHBAH was 19.3% in 2010-11[23]. Two specialised paediatric HIV clinics (Harriet Shezi Children's Clinic and the Perinatal HIV Research Unit (PHRU)) are located at CHBAH.

2.2.2 Charlotte Maxeke Johannesburg Academic Hospital (CMJAH)

This centrally-located hospital in Parktown, Johannesburg, has 1,088 beds and about 4,000 staff members. There are 58 general paediatric beds, 14 for haematology-oncology, 40 neonatal beds and 14 high-care neonatal beds. The 11-bed paediatric ICU caters for neonatal and paediatric critical care patients. A third of the 60,000 paediatric outpatients seen annually attend sub-specialty clinics. The paediatric HIV clinic at CMJAH had supervised approximately 2,000 children on ART as of February 2012 (personal communication: Dr S Varughese).

2.2.3 Rahima Moosa Mother and Child Hospital (RMMCH)

This maternity and paediatric hospital is located in Coronationville, in the western suburbs of Johannesburg. The paediatric department has 110 general beds and a six-bed ICU

for both neonatal and older children. 36,000 outpatients are seen annually, 15% of which attend sub-specialty clinics. Approximately 300 new HIV-positive patients presented to the RMMCH paediatric HIV clinic in 2011, a decrease from 440 patients in 2008. The HIV infection prevalence in the paediatric wards at RMMCH was 26% in 2010 (personal communication: Dr C Technau).

2.3 Study Population

The following inclusion criteria were used to derive the study population:

1. Positive cryptococcal antigen test and/or positive *Cryptococcus* culture on blood or CSF, and/or positive India ink test on CSF. For each patient only the first episode of cryptococcal disease was included;
2. Paediatric patients from birth to 14 years. The date of cryptococcal disease diagnosis from the NICD records , the date of admission and the birth dates from the medical records were used to determine the patients' ages;
3. Admitted to CHBAH, CMJAH or RMMCH in the period from 01 January 2002 through 31 December 2011;
4. Patient clinical data recorded by GERMS-SA surveillance programme;
5. Patient clinical notes available for review from the hospital records departments.

Exclusion criteria which were chosen so as to limit the study population to paediatric, rather than adult cases of cryptococcosis, and to optimise the completeness of study data included:

1. Children over 14 years of age;

2. Patient clinical notes missing.

2.4 Data Collection

The GERMS-SA database was used to retrieve details of the children that fitted the study inclusion criteria. Patient hospital files were sourced from the hospital records departments and the data collection form (Appendix 1, page 43-48) was used to obtain information for the study.

Weight-for-age Z-scores (WAZ) were calculated in children under 10 years of age using WHO AntroPlus Software (WHO, Geneva), and underweight was defined as being a WAZ greater than -3.0, but less than WAZ -2.0. Children were classified as being "severely underweight" if their WAZ was less than -3.0[24].

Immunologic status of the HIV positive children with available CD4 counts were classified according to the Centres for Disease Control and Prevention (CDC) immunologic classification system (Appendix 4, page 52) [25].

2.5: Data Analysis

Data were entered into an Excel spread sheet and thereafter imported into STATA version 12 (StataCorp, College Station, Texas) for analysis. Continuous data were described as means and standard deviations (SD) if normally distributed, or medians and interquartile ranges

(IQR) if skewed. The Student's t test was used to compare means, and the Wilcoxon rank sum test was used to compare medians.

Categorical data were described using frequencies and percentages, and proportions were compared using the Chi-square test or Fisher's exact test, as appropriate. Odds ratios and 95% confidence intervals (CI) were derived from the comparison of proportions between stratified groups.

In all statistical analyses, two-sided p-values <0.05 were considered to be statistically significant.

2.6: Ethics Clearance

The study was approved by the University of the Witwatersrand Human Research Ethics Committee (reference number: M120357; Appendix 2, page 49). Administrative bodies of the three study site hospitals gave permission to perform a retrospective review of the hospital records (Appendices 3, page 50-52). The study protocol was presented to the Department of Paediatrics Postgraduate committee, which approved it as adequate for the requirements of a Masters of Medicine dissertation.

3.0: Results

3.1: Demographics, HIV Status and Previous Medical History of the Cohort

Fifty-eight paediatric cases with laboratory-confirmed cryptococcal disease treated at Paediatric Departments in the three study facilities were reported to the GERMS-SA surveillance system over the 10-year study period. Five of the 58 patients were older than 14 years old and were thus excluded from the study. A further 5 patients were excluded from the study, because hospital records were lost and their clinical and outcomes data could not be described. There were therefore 48 patients included for analysis.

The majority (31/48; 64.6%) of the children with laboratory-confirmed cryptococcal disease were male. There were six infants in total: three one-month-old infants, two that were two-months-old and one nine month old. The median age of all the children in the study was 115.5 months (9.6 years; IQR, 7.0 to 11.8 years). The majority (27/48; 56.3%) of the study patients were from CHBAH, 16 (33.3%) were from CMJAH and five (10.4%) were from RMMCH.

One patient was admitted to ICU and 42 (87.5%) were admitted to general paediatric wards. The five remaining patients were reported to have been managed in hospital outpatient departments, without confirmation that they had been admitted to hospital for treatment.

3.1.1: HIV Prevalence within the study population

Forty-six (95.8%) patients had a documented HIV test and two had undefined HIV infection status. The majority (38/46, 82.6%) of the patients with defined HIV infection status were HIV-positive and the median age of the HIV positive children was 116.9 months (9.7 years; IQR, 7.7 to 12.0 years) . Twenty-seven (71.1%) of the HIV-positive patients had retrievable CD4 results, and the median CD4 count was 13 cells/mm^3 (IQR, 5 to 144 cells/mm^3). Most of the HIV-positive children with available CD4 counts were classified as being severely immunocompromised according to the CDC paediatric immunologic criteria (Table 1).

	<12 months	12-59 months	≥ 60 months	Total
No immunosuppression	0	0	0	0
Moderate immunosuppression	1 (50%)	0	4 (16.0%)	5 (18.5%)
Severe immunosuppression	1 (50%)	0	21 (84.0%)	22 (81.5%)
Number of children with available CD4 results	2	0	25	27

Table 1: Immunologic classification of HIV-positive children diagnosed as having laboratory-confirmed cryptococcal disease

Eighteen (47.4%) of the 38 HIV-positive children were on ART at the time of hospitalisation with their cryptococcal illness. The median CD4 count in HIV-positive children on ART (n=15; 48 cells/mm^3; IQR, 10 to 289 cells/mm^3) was significantly higher than the median CD4 count of those not yet on ART (n=12; 7 cells/mm^3; IQR, 5 to 23 cells/mm^3), P=0.034.

Of the eight HIV-negative patients, three were infants under one year of age and one had a malignancy. The median age of the HIV-negative children in the study was 82.7 months (6.9 years; IQR, 0.2 to 11.2 years).The underlying predisposing conditions for five of the HIV-negative patients with cryptococcosis could not be determined by review of the clinical folders and three of these five were on anti-TB treatment during their admission.

	Age	Gender	Length of Hospital Stay (days)	Site of Cryptococcal Infection	Antifungal Treatment Administered	Concurrent TB	Predisposing Conditions	Outcom
1	6 years	M	150	Blood	Fluc	No	Malignancy (ALL)	D/C
2	9 years	M	3	Blood and CSF	None	Yes	Undetermined	Died
3	12 years	M	21	CSF	Ampho B Fluc	No	Undetermined	RHT
4	11 years	M	5	CSF	None	Yes	Undetermined	D/C
5	6 years	M	60	Blood and CSF	Ampho B Fluc	Yes	Undetermined	D/C
6	2 months	F	12	CSF	None	No	Undetermined	D/C
7	1 month	M	1	CSF	None	No	Neonate	D/C
8	1 month	M	21	CSF	Ampho B Fluc	No	Premature	T/F

Table 2: Clinical characteristics of eight HIV-negative children with laboratory-confirmed cryptococcosis

F: female; **M:** male;

CSF: cerebrospinal fluid; **TB:** tuberculosis

Ampho B: Amphotericin B; **Fluc:** Fluconazole

Rx: Treatment; ALL**:** Acute lymphoblastic leukaemia

D/C: Discharged; **T/F:** Transferred to another facility

RHT: Refusal of hospital treatment

Most of the HIV-negative children (7/8, 87.5%) had cryptococcal meningitis and one had cryptococcal fungaemia without meningitis. Half of these patients were treated for cryptococcosis and one out of the eight (12.5%) died. The clinical characteristics of the HIV-negative children with laboratory-confirmed cryptococcal disease are summarised in Table 2.

3.1.2 Previous Hospitalisation History

Twenty five (52.1%) of the 48 paediatric laboratory-confirmed cryptococcal disease patients had never been hospitalised before. Their median age was 108.6 months (9.1 years; IQR, 6.5 to 11.0 years), and 17 (68.0%) were HIV-positive. The median CD4 count in the HIV-positive children who had never been hospitalised before was 10 cells/mm^3 (IQR, 6 to 34 cells/mm^3). ART status was known in 16 of the HIV-positive children who had never previously been hospitalised, and of those seven (41.2%) were on ART and nine (52.9%) were not on ART.

Nineteen (39.6%) of the 48 patients included in the study had a history of one previous hospitalisation, of which 18 (94.7%) were HIV-positive. Four (8.3%) of the 48 study patients had more than two previous admissions, and three (75%) of them were HIV-positive. The HIV-negative child who had had more than two previous hospitalisations was on TB treatment but no condition predisposing to cryptococcal disease could be determined in this child.

3.2: Clinical Presentation

3.2.1 Anthropometric Parameters

The study population was generally malnourished, with a median WAZ of -2.98 (IQR, -3.53 to -1.74). The median WAZ in HIV-positive children was -2.99 (IQR, -3.53 to -1.80), compared to -1.80 (IQR, -3.68 to -1.54) in HIV-negative children, P=0.451. Overall, only three (10.3%) of the 29 children whose WAZ could be calculated had normal nutritional status. Numbers were too small to derive statistical significance in terms of degree of malnutrition, stratified by HIV infection status.

3.2.2 Clinical Parameters at Admission

The most common presenting symptoms were headache (23/38: 60.5%) and vomiting (22/37: 59.5%). Other symptoms mentioned in the history at presentation were fever (16/37: 43.2%), seizures (9/37: 24.3%) and altered mental status (5/37: 13.5%) (Table 3).

Axillary temperature at presentation was recorded in 42 patients, and 13 (31%) had fever (defined as a temperature >37.5 ˚C). The median temperature was 37.0 ˚C (IQR, 36.0 to 38.0 ˚C). The median temperature at presentation in febrile patients was 38.0 ˚C (IQR, 38.0 to 39.0 ˚C) (Table 3).

The Glasgow Coma Scale (GCS) was recorded in 35 (72.9%) of the patients, and of these 33 (94.3%) were scored as being 15/15. The two children with GCS less than 15 were HIV-positive: a girl of 123 months (10 years) and a boy of 160.6 months (13 years). Both presented with headache, meningism and altered mental status. The girl was severely

immunocompromised (CD4 count, 7 cells/mm^3) and was initiated onto ART during the admission. The boy had previously defaulted ART and had been restarted onto therapy, but his intercurrent CD4 count was 289 cells/mm^3 (severe immunosuppression). The girl had cryptococcal fungaemia and meningitis whilst the boy had cryptococcal meningitis. They each had more than one lumbar puncture done during their admission, and both had admission durations of longer than 21 days.

Details regarding the presence or absence of photophobia was available in 35 (72.9%) of the patient folders, and seven (20%) of these patients presented with photophobia (Table 3).

Nineteen (52.8%), of the 36 with a note on meningeal irritation in their clinical files, had meningism. Papilloedema was observed in one (5%) of 20 children in whose clinical notes this clinical finding was reported. Focal signs were present in five (13.5%) of 37 patients (three patients had 6^{th} nerve palsy, one had 7^{th} nerve palsy and one had left arm weakness). The lumbar puncture opening pressure was recorded in 12 (25%) of the 48 children with laboratory-confirmed cryptococcosis, and of these 4 (33.3%) had a mean opening pressure of greater than 25 centimetres of water (Table 3).

Medical History						
		Total (n=48)	**HIV positive (n=38)**	**HIV negative (n=8)**	**HIV unknown (n=2)**	**OR (95% CI); P-value***
First Admission		25 (52.1%)	17 (44.7%)	6 (75.0%)	2 (100.0%)	3.71 (0.55-40.98); 0.243^
Previous Hospitalisation		23 (47.9%)	21 (55.3%)	2 (25.0%)	0	
Presenting Symptoms and Signs						
		Total	**HIV positive**	**HIV negative**	**HIV unknown**	**OR (95% CI); P-value***
Fever (n=37)		16 (43.2%)	13 (44.8%)	3 (37.5%)	0	1.35 (0.21-10.31); 0.711
Headache (n=38)		23 (60.5%)	21 (30.0%)	2 (25.0%)	0	7.00 (0.95-79.19); 0.039^
Vomiting (n=37)		22 (59.5%)	17 (58.6%)	5 (62.5%)	0	0.85 (0.11-5.42); 1.000^
Seizures (n=37)		9 (24.3%)	8 (27.6%)	1 (12.5%)	0	2.66 (0.26-134.97); 0.649^
Altered mental status (n=37)		5 (13.5%)	4 (13.8%)	1 (12.5%)	0	1.12 (0.09-62.93); 1.000^
GCS (n=35)	GCS<15/15	2 (5.7%)	2 (5.3%)	0	0	1.000^
	GCS 15/15	33 (94.3%)	26 (92.9%)	6 (100.0%)	1 (100.0%)	
Meningism (n=36)		19 (52.8%)	16 (53.3%)	3 (50.0%)	0	1.14 (0.13-9.94); 1.000^
Photophobia (n=35)		7 (20.0%)	6 (21.4%)	1 (14.3%)	0	1.63 (0.14-87.63); 1.000^
Papilloedema (n=20)		1 (5%)	0	1 (25.0%)	0	0.200^
Focal signs (n=37)		5 (13.5%)	4 (13.8%)	1 (12.5%)	0	1.12 (0.09-62.93); 1.000^
LP opening pressure (cm H_2O)	>25	4 (33.3%)	3 (27.3%)	1 (100.0%)	0	0.333^
	≤25	8 (66.7%)	8 (72.7%)	0	0	

Table 3: Clinical presentation of children with laboratory-confirmed cryptococcosis

* P-values relate to the comparison of proportions between HIV positive and HIV negative children.

^ Fisher's exact test.

3.2.3 Disease syndromes in the study population

Twenty-four (50.0%) of the 48 patients had cryptococcal meningitis, 14 (29.2%) had cryptococcal meningitis with concomitant cryptococcaemia, and 10 (20.8%) had cryptococcal fungaemia without meningitis (Table 4). Apart from meningism, which was significantly more frequently observed in children with *Cryptococcus* cultured on CSF samples compared to those who had culture-negative CSF specimens, the clinical presentation of children with laboratory-confirmed cryptococcal disease was similar regardless of cryptococcal syndrome (Table 4).

Presenting Symptoms and Signs		Total	Cryptococcal Fungaemia (n=10)	Dual Meningitis & Fungaemia (n=14)	Cryptococcal Meningitis (n=24)	OR (95% CI); P-value*
First Admission		25 (52.1%)	8 (80.0%)	8 (57.4%)	9 (37.5%)	0.20 (0.02-1.24); 0.075^
Previous Hospitalisation		23 (47.9%)	2 (20.0%)	6 (42.9%)	15 (62.5%)	
Fever (n=37)		16 (43.2%)	5/7 (71.4%)	5/12 (41.7%)	6/18 (33.3%)	0.23 (0.02-1.78); 0.202^
Headache (n=38)		23 (60.5%)	2 (28.6%)	8 (61.5%)	13 (72.2%)	5.25 (0.68-61.27); 0.089^
Vomiting (n=37)		22 (59.5%)	4 (66.7%)	8 (61.5%)	10 (55.6%)	0.69 (0.06-5.77); 1.000^
Seizures (n=37)		9 (24.3%)	1 (16.7%)	3 (23.1%)	5 (27.8%)	1.74 (0.15-92.38); 1.000^
Altered mental status (n=37)		5 (13.5%)	0	3 (23.1%)	2 (11.1%)	0.567^
GCS (n=35)	GCS<15/15	2 (5.7%)	0	1 (10.0%)	1 (5.6%)	1.000^
	GCS 15/15	33 (94.3%)	7 (100.0%)	9 (90.0%)	17 (94.4%)	
Meningism (n=36)		19 (52.8%)	0	8 (61.5%)	11 (64.7%)	0.006^
Photophobia (n=35)		7 (20.0%)	0	2 (18.2%)	5 (29.4%)	0.306^
Papilloedema (n=20)		1 (5.0%)	0	0	1 (8.3%)	-^
Focal signs (n=37)		5 (13.5%)	0	1 (7.7%)	4 (22.2%)	0.567^
LP opening pressure (cm H2O)	>25	4 (33.3%)	0	1 (20.0%)	3 (50.0%)	1.000^
	≤25	8 (66.7%)	0	4 (80.0%)	3 (50.0%)	

Table 4: Clinical presentation and spectrum of cryptococcal disease in the study population

* P-values relate to the comparison of proportions between cryptococcal meningitis cases (with or without cryptococcaemia) and cases with cryptococcaemia only.

^ Fisher's exact test.

3.2.4 Concurrent Diagnoses in the study population

Nineteen (39.6%) patients were started on anti-tuberculosis treatment during the course of their hospitalisation with laboratory-confirmed cryptococcosis. Three (15.8%) of the children initiated on anti-tuberculosis treatment were diagnosed as having tuberculous meningitis, all of whom were HIV- positive.

Thirteen (27.1%) children were treated empirically for concomitant bacterial meningitis. Of these 13 patients, ten (77.0%) were HIV-positive and three HIV-negative.

Numbers were too small to meaningfully compare CSF pleocytosis and biochemical parameters stratified by meningitis type, although there was a trend for children diagnosed with TBM to have a higher CSF protein (all three children diagnosed as having TBM had a CSF protein greater than 0.50 g/L) compared to those with bacterial meningitis (2/8 (25.0%) had a CSF protein greater than 0.50 g/L; P=0.061, exact).

3.3: Cryptococcal Treatment Regimens Used to Treat Children with Laboratory-confirmed Cryptococcosis

Treatment regimens used in the management of the children was available upon review of 45 (93.8%) of the clinical folders. Thirty-two (71.1%) of these 45 patients received amphotericin B for a median of 14 days (IQR, 10.5 to 26 days) at a median dose of 1.0 mg/kg/day (IQR, 1.0 to 1.1 mg/kg/day), and 13 (28.9%) patients received no amphotericin B.

Eighteen (75.0%) of the 24 patients with isolated cryptococcal meningitis and 11 (78.6%) of the 14 with dual fungaemia and meningitis were treated with amphotericin B, respectively. By contrast, three (30.0%) of the 10 children with cryptococcaemia without cryptococcal meningitis were treated with amphotericin B. Therefore, children with cryptococcal meningitis were 7.5-fold (95% CI, 1.31 to 51.93) more likely to have been treated with amphotericin B compared to those who had fungaemia without meningitis, P=0.001 (exact).

Fluconazole was administered to 28 (62.2%) of the patients with available treatment data, for a median 14 days (IQR, 7.5 to 21 days) at a median dose of 10.4 mg/kg/day (IQR, 6.3 to 16.0 mg/kg/day). Five (41.7%) of the 12 children on fluconazole and concomitant TB treatment were on boosted fluconazole dosage regimens (i.e., >10 mg/kg/day). At discharge 28 (62.2%) patients were on fluconazole prophylaxis. Of the 18 children discharged home without fluconazole prophylaxis, 12 (66.7%) were HIV-positive.

Ten children in the study population (22.2% of those with available treatment data) did not receive any anti-fungal therapy during their admission for cryptococcosis. The median age of these 10 children was 107 months (8.9 years; IQR, 0.2 to 11.0 years). Five of them were HIV positive, 4 were HIV negative and the HIV status of one child was unknown. Six of these children died during their admission and the other 4 were discharged home.

3.4: Outcomes

The median duration of hospital stay of the study patients was 20 days (IQR, 11 to 34 days). Thirty-three (68.8%) patients were discharged home and the majority of these (28/33, 84.8%) were followed up after discharge. The outcome of three patients was unknown: the

parents of two of these (whose ages were 6yrs (HIV-positive, pre-ART) and 12yrs (HIV-negative) refused further hospital treatment during their admission and left the hospital against medical advice, and the records of the other two patients (ages 11 (HIV-unknown) and 12 (HIV-positive, unknown ART status), did not specify any outcome at all.

Duration of hospital stay for the two patients whose parents refused further hospital treatment were 18 and 21 days, respectively. Three of the four patients with unknown outcome had been diagnosed with cryptococcal meningitis and the fourth patient had not had a lumbar puncture because of thrombocytopaenia at admission, and was diagnosed with cryptococcal fungaemia without meningitis. Amphotericin B and fluconazole therapy were administered to two of the four patients during admission; however the treatment details of the other two patients were not specified.

Ten (20.8%) of the 48 patients included in this study population died during the course of their hospital admission (Table 5). The majority (9/10) of these patients were 84 months (7 years) and older and one patient was 30.8 months (2.5 years) old. Half of the children who died were being admitted for the second time to hospital and their median duration of hospitalisation was two days (IQR, 1 to 5 days). Nine of the children who died were HIV-positive, and only 2/9 (22.2%) of these were on ART. Amongst HIV-positive children, the odds of dying were 4.7-fold (95% CI, 0.68-51.75) higher in those not on ART compare to those who had accessed ART, P=0.125 (exact).

Two of the ten patients that died had cryptococcal meningitis without fungaemia, four (40%) had both cryptococcal fungaemia and meningitis and four (40%) had cryptococcal fungaemia without meningitis. The odds of dying were 5.5-fold (95% CI, 0.89-57.95) greater in children with cryptococcaemia compared to those who had meningitis but who were blood culture negative for *Cryptococcus*, P=0.072. Of the four patients with both cryptococcal

fungaemia and meningitis, two received amphotericin B and fluconazole therapy and one received amphotericin B only as therapy before he died.

The majority (7/10) of the children who died during admission with cryptococcal disease were also being treated for tuberculosis and one patient had previously completed anti-TB treatment.

Six of the patients who demised did not receive any anti-fungal therapy for cryptococcal disease, and they died at a median of 2 days (IQR, 1 to 3 days) into their hospital stay.

Age (months)	Gender	Admission number	Duration of Hospital stay (days)	HIV Status	CD4 Count (cells/mm^3)	On ART	Type of Cryptococcal Disease	Treatment Given		
								Amphotericin B	Fluconazole	TB Rx
30.8	M	2	5	Pos	Unknown	N	C	N	N	N
84	M	2	66	Pos	Unknown	Y	B/C	Y	Y	Y
89	M	2	2	Pos	Unknown	N	B/C	Y	N	Y
105	F	1	2	Pos	1	Y	B	N	N	Y
108	F	1	2	Pos	Unknown	N	B	N	N	Y
131	M	2	1	Pos	Unknown	N	C	N	N	Y
144	M	1	11	Pos	2	N	B/C	Y	Y	Y
165	F	2	1	Pos	4	N	B	N	N	Y
84	M	1	1	Neg	N/A	N/A	B	U	U	N
124	M	1	3	Neg	N/A	N/A	B/C	N	N	Y

Table 5: Characteristics of the ten patients that demised in the study population

ART=antiretroviral therapy

F=female

M=male

Neg=negative

Pos=positive

N/A=not applicable

Y=yes; **N**=no; **U**=unknown

B=blood

C=cerebrospinal fluid

B/C= blood and cerebrospinal fluid

4.0: Discussion

4.1 Summary of Study Findings

This study describes the spectrum of culture-confirmed cryptococcal disease in children managed at three teaching hospitals in Johannesburg over a ten-year period. Fifty-eight children, the majority of whom were HIV-positive with severe immunosuppression, were identified through a well-established laboratory surveillance network; however, 48 were included in the analysis. The median age of the 48 children was 9.6 years and they were generally malnourished.

Thirty-eight of the children had cryptococcal meningitis with or without concomitant cryptococcaemia, and 10 had cryptococcal sepsis without meningitis. The children with cryptococcal meningitis were more likely to have been treated with amphotericin B compared to those who had fungaemia without meningitis. Almost 40% of the children in the study were started on anti-tuberculosis treatment during the course of their hospitalisation with culture-confirmed cryptococcosis. The median hospital stay of the study patients was 20 days, the majority of them were discharged home and 20% died.

The majority (38/48) of the children were HIV positive, 22 of which had severe immunosuppression. Although HIV infection was the most prevalent underlying predisposing factor for cryptococcal disease in this study population, risk factors for cryptococcal disease in the HIV-negative children included infancy (n=3) and leukaemia (n=1). The underlying predisposing conditions for five patients could not be determined by review of the clinical folders. Most of the HIV-negative children (n=8) had cryptococcal meningitis and one had cryptococcal sepsis without meningitis. Half of these patients were treated for cryptococcus and one out of the eight died.

4.2 Comparison of Study Findings to the Published Literature

A study done from 42 United States children's hospitals between 2003 and 2008 identified 63 children admitted for the treatment of cryptococcal infection with the majority of paediatric cryptococcosis occurring in HIV negative patients. However, most patients had other immunocompromising medical conditions [21].

Closer to home in Harare, Zimbabwe the records of 13 HIV positive children (≤16 years) diagnosed with cryptococcal meningitis between 1995 and 2000 were reviewed in a study designed to elucidate features unique to paediatric disease [ref]. The children were compared with adult patients with HIV-associated cryptococcal meningitis. Cryptococcal meningitis in these African children presented acutely or subacutely and with a fulminant picture consistent with progressive meningoencephalitis in the background of severe immune compromise [18].

A comparison of 16,192 incident cases of cryptococcosis detected through population-based surveillance was performed from 2005–2007 in South Africa, with 361 (2%) episodes occurring among children. This series of 361 cases of paediatric cryptococcosis is one of the largest described to date and most children (64%) and adults (63%) were severely immunocompromised at the time of diagnosis [17].

From the literature and this study, it is evident that paediatric cryptococcosis is a rare condition but that it should be considered in children who are severely immunocompromised (and in Southern Africa) especially in the HIV positive paediatric population.

4.3 Areas Identified in which Clinical Management deviated from Published Guidelines

This study highlighted certain areas in which local practice deviates markedly from published guidelines. These centred mostly on the pharmacokinetics of fluconazole and drug-drug interactions between this agent and rifampicin.

Rifampicin activates hepatic clearance of fluconazole, so children on fluconazole and anti-TB treatment together end up with suboptimal fluconazole drug levels if the fluconazole dose is not boosted [11, 20]. In this study five (41.7%) of the 12 children on fluconazole and concomitant TB treatment were on boosted fluconazole dosage regimens (i.e., >10 mg/kg/day), although published guidelines recommend that patients on dual fluconazole and rifampicin therapy ought to be treated with an optimised (15 mg/kg/day) dose of fluconazole [ref HIV Clinicians Society Guidelines]. At discharge, 28 (62.2%) patients were on fluconazole prophylaxis. Of the 18 children discharged home without fluconazole prophylaxis, 12 (66.7%) were HIV-positive. These patients with cryptococcosis received suboptimal care as a result of the fluconazole therapy that was deviant from published guidelines.

Ten (20.8%) of the 48 patients in the study population died during the course of their hospital admission. Six of these patients (60%) did not receive any anti-fungal therapy for cryptococcal infection, and they died at a median of 2 days (IQR, 1 to 3 days) into their hospital stay. Five of these six patients that were not on anti-fungal therapy were HIV-positive and only one of them was on ART. This may highlight the fact that cryptococcal disease is not often considered in part of the differential diagnosis at admission in ill children presenting at our public sector health facilities.

There needs to be a high index of suspicion for cryptococcosis in HIV-positive children with severe immune-compromise and anti-fungal therapy and ART should be instituted timeously as per guidelines.

4.4 Study Limitations

The retrospective nature of this study was a limitation as there were some incomplete data from patients' notes as recorded by the treating clinicians. The clinical parameters looked at in the study population's clinical files were incompletely recorded. Forty-six (95.8%) patients had a documented HIV test and two had undefined HIV-infection status. The underlying predisposing conditions for five of the eight HIV-negative cryptococcal patients could not be determined by review of the clinical records.

The study was performed in three hospitals in Johannesburg and the sample size (n=48) was small which would have impacted on our ability to draw statistically relevant inferences from the data.

5.0: Conclusion and Recommendation

Paediatric cryptococcosis is a rare condition. In South Africa, HIV infection is an important predisposing condition to cryptococcal infection. There appeared to be widespread deviation from published guidelines in terms of treating patients with fluconazole at public health facilities in Gauteng Province. Clinicians caring for children with cryptococcal disease should seek advice from infectious disease clinicians in order to optimise patient care.

Appendices

Appendix 1: Data Collection Tool

CFR start date:	**CFR finalised date:**
Sources of data: **GERMS database/Medical records**	**Research case number:**
Hospital: **CHBAH** **CMJAH** **RMMCH**	**Ward:**
Date of Birth: **Age:** **Months** **Years**	**Gender:** **Male** **Female** **Unknown**
Date of admission:	**Number of previous hospital admissions:**
Is patient referred from another hospital? **Yes/ No/ Unk If Yes specify:**	**Was patient transferred to another hospital?** **Yes/ No/ Unk If yes specify:**

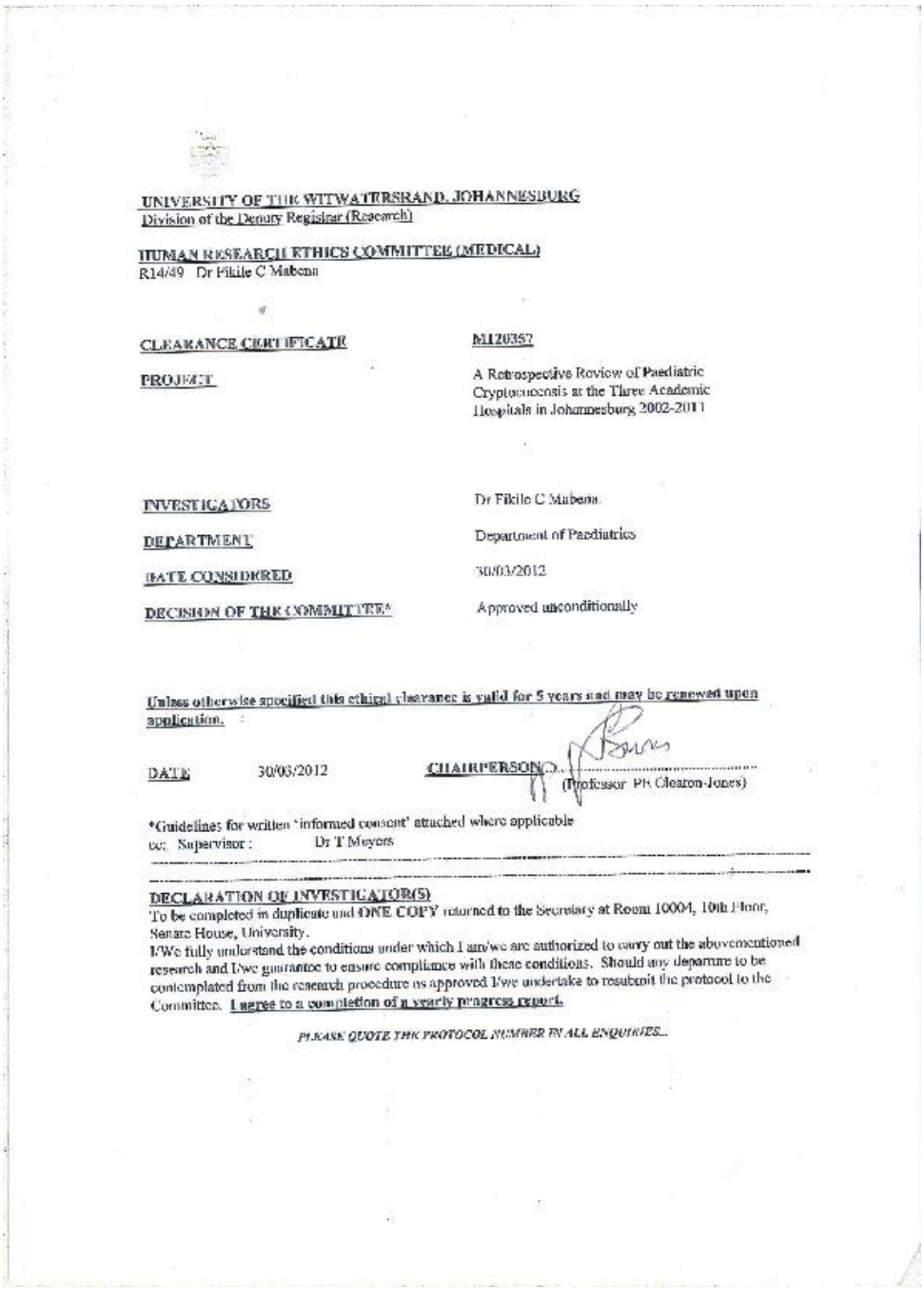
Presenting history:	**Clinical examination:**
Main complaint: **Fever: Yes/No/Unk** **Headache: Yes/No/Unk** **Altered mental state: Yes/No/Unk** **Vomiting: Yes/No/Unk** **Seizures: Yes/No/Unk** **Photophobia: Yes/No/Unk** **Other: Yes/No/Unk If Yes specify:**	**Fever: Yes/No/Unk** **Temp:** **Papilloedema: Yes/No/Unk** **Meningism: Yes/No/Unk** **GSC:** **Altered mental status: Yes/ No/Unk** **Focal signs: Yes/No/Unk If Yes specify** **LP opening pressure done: Yes/No/Unk** **If Yes specify OP (in cm H2O)** **Other CNS signs: Yes/No/Unk** **If Yes expand:** **Other systems normal: Yes/No/Unk** **If No expand:**
Differential diagnosis: **Bacterial meningitis: Yes/No/Unk** **TB meningitis: Yes/No/Unk** **Other:**	**Site of specimen collection:** **CSF Blood Other:** **Date of specimen collection:** **Lab specimen number:**

Was this the first episode of cryptococcosis? **Yes/No/Unk If Yes When?**	**If No, what was the treatment used during** **Previous admission?** **Ampho B Fluconazole Other:**
Treatment used in current admission: **Amphotericin B: Yes/No/Unk** **Dose:** **Duration:** **Fluconazole: Yes/No/Unk** **Dose:** **Duration:** **Other:**	**Weight @ diagnosis:**
Duration of stay in hospital: **Admission date:** **Discharge date:**	**On discharge did patient receive** **fluconazole: Yes/No/Unk** **Weight: Dose:**

CSF results (related to diagnosis): **Cell count:** **Chemistry:** **Microscopy: gram and India ink:** **Cryptococcal antigen test:** **Bacterial culture:** **Fungal culture:** **TB culture:** **Other:** **Number of LP's done:**	**Last CSF results:** **Cell count:** **Chemistry:** **Microscopy:** **Cryptococcal antigen:** **Bacterial culture:** **Fungal culture:** **TB culture:** **Other:**
Patients on Ampho B: **U+E results on admission:** **U+E results @ discharge:**	**Patients on Ampho B:** **U+E/Hb/Mg monitored 2x or more during** **admission: Yes/No/Unk If Yes specify**
Was patient tested for HIV? Yes/No/Unk **If Yes, HIV status:** **Positive/Negative/Unknown**	**For HIV-infected patients: ART use:** **Perinatal: Yes/No/Unk** **ART: Yes/No/Unk**
CD4 count at admission:	**Last CD4 count:**

Viral load at admission:	**Last Viral load:**
Other conditions predisposing patient to infection (apart from HIV): **Malignancy:** **Organ transplant:** **Steroid use:** **Unknown:** **Other(specify):**	**Confirmed TB: Yes/No/Unk** **Current TB treatment:** **Previous TB treatment:**
Radiological studies: **CXR/CT Brain/Other** **Radiological findings:**	**For patients who were discharged:** **Neurological status @ discharge:** **Intact/ Unknown/Not Intact Specify:**
Data collector:	**Patient outcome:** **Discharged: Home/Follow Up/Unknown** **Died:** **Absconded/RHT:** **Unknown:**

Appendix 2: Ethics Clearance Certificate



UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Fikile C Mabena

CLEARANCE CERTIFICATE	M120357
PROJECT	A Retrospective Review of Paediatric Cryptococcosis at the Three Academic Hospitals in Johannesburg 2002-2011
INVESTIGATORS	Dr Fikile C Mabena
DEPARTMENT	Department of Paediatrics
DATE CONSIDERED	30/03/2012
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

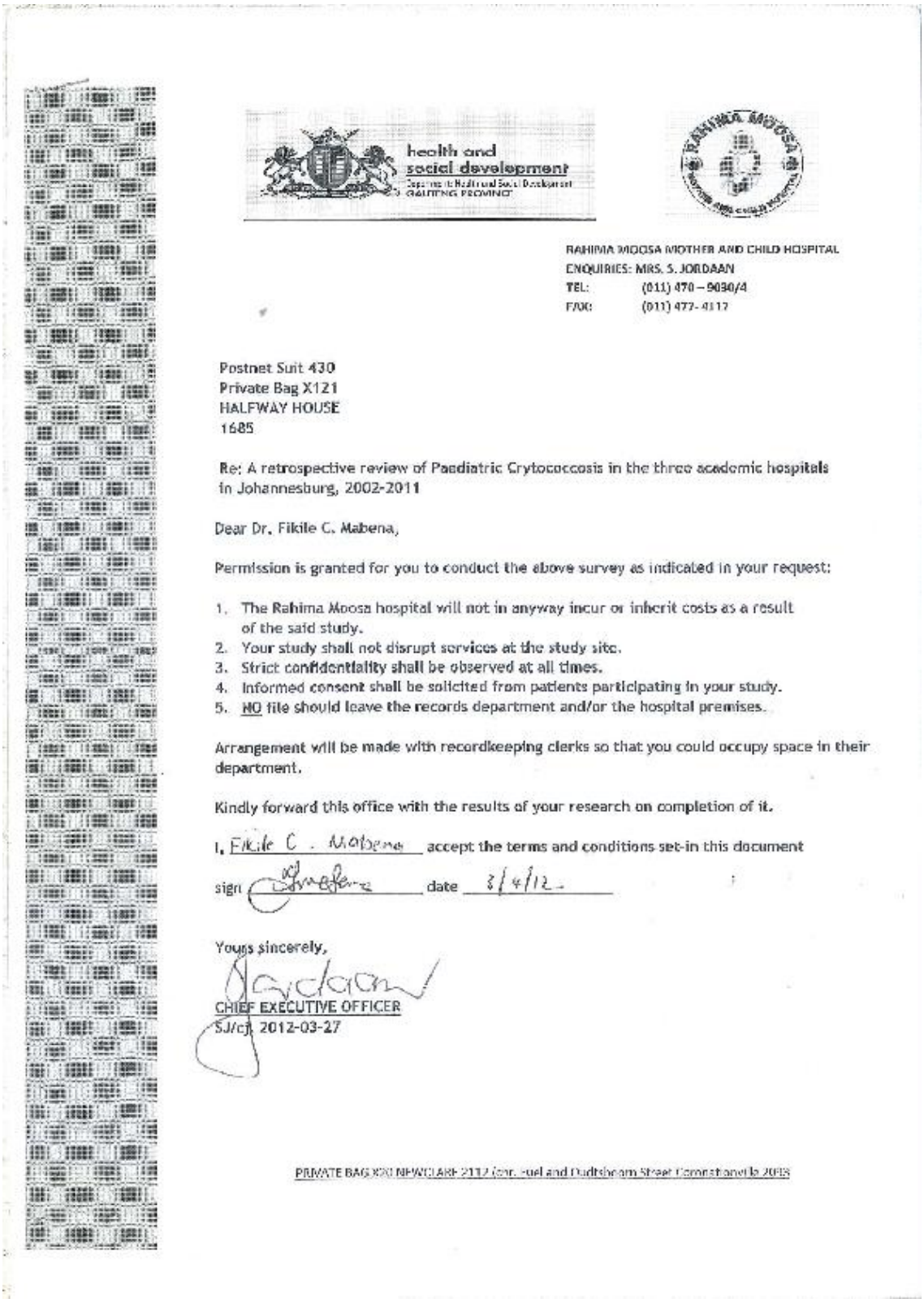
DATE 30/03/2012 CHAIRPERSON .....
(Professor PR Clearon-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr T Meyers

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and ONE COPY returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. I agree to a completion of a yearly progress report.

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES.

Appendix 3: Hospital Permission Letters



health and social development
Department of Health and Social Development
GAUTENG PROVINCE

RAHIMA MOOSA MOTHER AND CHILD HOSPITAL
ENQUIRIES: MRS. S. JORDAAN
TEL: (011) 470 – 9030/4
FAX: (011) 477- 4117

Postnet Suit 430
Private Bag X121
HALFWAY HOUSE
1685

Re: A retrospective review of Paediatric Crytococcosis in the three academic hospitals in Johannesburg, 2002-2011

Dear Dr. Fikile C. Mabena,

Permission is granted for you to conduct the above survey as indicated in your request:

1. The Rahima Moosa hospital will not in anyway incur or inherit costs as a result of the said study.
2. Your study shall not disrupt services at the study site.
3. Strict confidentiality shall be observed at all times.
4. Informed consent shall be solicited from patients participating in your study.
5. NO file should leave the records department and/or the hospital premises.

Arrangement will be made with recordkeeping clerks so that you could occupy space in their department.

Kindly forward this office with the results of your research on completion of it.

I, Fikile C. Mabena accept the terms and conditions set-in this document

sign [signature] date 3/4/12.

Yours sincerely,

[signature]
CHIEF EXECUTIVE OFFICER
SJ/cj, 2012-03-27

PRIVATE BAG X20 NEWCLARE 2112 (cnr. Fuel and Outshoorn Street Constantia Kloof)

health and social development
Department: Health and Social Development
GAUTENG PROVINCE

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Maureen Motjelele
Office of the Chief Executive Officer
Tell: 011 488 3793\2
Email:Maureen.Motjelele@gauteng.gov.za
14 March 2012

Fikile C.Mabena
Paediatrics Department
CMJAH

Dear Ms .Mabena

RE: Request for permission to conduct a study on" A retrospective review of paediatrics erysipelas in the three academic hospitals in Johannesburg, 2002-2011.

Please note that your above request to conduct a research is provisionally approved, please note that your study can only commence once ethics committee approval is obtained.

Yours sincerely

Dr T. E. SELEBANO
Chief Executive Officer

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 06 March 2012

TITLE OF PROJECT: A case series of cryptococcosis in paediatric patients at the three academic hospitals in Johannesburg, 2002 - 2011

UNIVERSITY: Witwatersrand:

Received by:

Date 3/4/12

Principal Investigator: Dr F Mabena

Department: Paediatrics

Supervisor (If relevant): Dr T Meyers and Dr N Govender

Permission Head Department (where research conducted): Yes

Date of start of proposed study: 1 April 2012

Date of completion of data collection: 31 December 2012

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Hospital. The CEO /management of Chris Hani Baragwanath Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.
- the Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- the MAC will be informed of any serious adverse events as soon as they occur
- permission is granted for the duration of the Ethics Committee approval.

.....

Recommended

(On behalf of the MAC)

Date: 06 March 2012

.....

DR. P. LINGHAM

Dep CEO

Approved/~~Not Approved~~

Hospital Management

Date: 08 MAR 2012

Appendix 4: CDC HIV Immunologic Classification Table

Immunologic categories based on age-specific CD4+ T-lymphocyte counts and percent of total lymphocytes

Immunologic category	**Age of child**					
	<12 mnths		**1–5 yrs**		**6–12 yrs**	
	μL	**(%)**	**μL**	**(%)**	**μL**	**(%)**
1: No evidence of suppression	≥1,500	(≥25)	≥1,000	(≥25)	≥500	(≥25)
2: Evidence of moderate suppression	750–1,499	(15–24)	500–999	(15–24)	200–499	(15–24)
3: Severe suppression	<750	(<15)	<500	(<15)	<200	(<15)

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